



# Outcome of Lung Transplantation as a Treatment of Patients With Chronic Obstructive Pulmonary Disease: A Single-Center Study

Magdalena Latos<sup>a,b,\*</sup>, Mirosław Nęcki<sup>b</sup>, Daria Pawlak<sup>a</sup>, Maciej Urlik<sup>b</sup>, Remigiusz Antończyk<sup>a,b</sup>, Marek Ochman<sup>a,b</sup>, Marta Wajda Pokrontka<sup>a</sup>, Monika Wojtasik<sup>a</sup>, Piotr Przybyłowski<sup>b,c</sup>, Marian Zembala<sup>a,b</sup>, and Tomasz Stącel<sup>b</sup>

<sup>a</sup>Department of Cardiac, Vascular and Endovascular Surgery and Transplantology, Medical University of Silesia, Katowice, Poland;

<sup>b</sup>Silesian Center for Heart Diseases, Zabrze, Poland; and <sup>c</sup>First Chair of General Surgery Jagiellonian University, Medical College, Kraków, Zabrze, Poland

## ABSTRACT

**Background.** Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide. Lung transplantation (LTx) is often the only therapeutic option for patients with end-stage COPD. The aim of the study was to establish whether patients with end-stage COPD benefited from lung transplantation and assess the pulmonary function by the 6-Minute Walk Test (6MWT) and forced expiratory volume in 1 second (FEV1).

**Methods.** A retrospective study was carried out in the group of 69 patients (40 recipients, 18 patients currently waiting, and 11 patients who died while waiting for a lung graft) diagnosed with end-stage COPD, referred to the Silesian Center for Heart Diseases' Lung Transplant Ward, and qualified to be treated by means of lung transplantation between 2006 and 2018. The beginning of the observation for all 69 patients was a qualification date.

**Results.** Kaplan-Meier estimation determined that graft recipients noted 50% probability of survival at approximately 5.5 years, whereas patients from the other group had such parameters at about 1.4 years. The average results FEV1 obtained at qualification were 23.69% for single lung transplantation (SLT); and 22.06% for double lung transplantation (DLT). Average patient acquired 158.07m in the 6MWT. One year after procedure the average values of FEV1 were SLT, 55.83%; DLT, 79.54%; and 430.7 m in the 6MWT overall.

**Conclusions.** Qualified patients who underwent lung transplantation lived longer than those who did not undergo such a procedure. We observed a difference in SLT and DLT recipients.

**C**HRONIC obstructive pulmonary disease (COPD) is associated with a large economic, social, and health-care burden worldwide [1]. COPD is the fourth leading cause of death in the world, [2] but the incidence rate is projected to increase in the coming decades because of continued exposure to COPD risk factors and aging of the population [3]. According to World Health Organization (WHO) estimates, 65 million people have moderate to severe COPD [4]. Such a common disease necessitates that prevention of COPD should be a major public health goal [5]. The most essential step in any treatment plan for COPD is smoking cessation and nicotine replacement. Regarding pharmacotherapy there are basically 5 categories of

medications commonly used in the treatment of COPD [6]. For patients with hypoxemia due to advanced COPD, domiciliary oxygen therapy is frequently prescribed [7]. Despite the possibility of drug treatment, COPD is the most common indication for lung transplantation in adults [8]. According to the International Society for Heart and Lung Transplantation (ISHLT) registry, it represents 30.1% of all

\*Address correspondence to Magdalena Latos, MD, Medical University of Silesia, Silesian Centre for Heart Diseases ul. Marii Skłodowskiej-Curie 9 Pawilon C, 41-800 Zabrze, Poland. Tel: (+48) 667 288 893. E-mail: [latos.magdalena93@gmail.com](mailto:latos.magdalena93@gmail.com)

lung transplantations performed from 1995-2018 [8]. The criteria for referring patients for lung transplantation are established in the guidelines developed by ISHLT and include:

- Clinically and physiologically severe disease for which medical therapy is ineffective or unavailable
- The risk of death from lung disease without transplantation is >50% within 2 years
- The likelihood of surviving at least 90 days after lung transplantation is >80%
- Absence of nonpulmonary medical comorbidity that would be expected to limit life expectancy substantially in the first 5 years after transplantation
- Satisfactory psychosocial profile and support system [9]

After qualification, the patient is reported to the lung transplant waiting list [10]. While waiting for a lung graft, COPD patients should remain in pulmonary rehabilitation to preserve their physical conditioning and optimize their post-transplant potential for recovery [11]. ISHLT has published a consensus statement, which recommends the following factors be used when considering the timing for the transplantation of a COPD patient to a lung transplant facility:

- Forced expiratory volume in 1 second (FEV1) below 15% to 20% of predicted value
- BODE index (for Body mass index, airflow Obstruction, Dyspnea, and Exercise) greater than or equal to 7
- Three or more severe exacerbations during the preceding year
- One severe exacerbation with acute hypercapnic respiratory failure, moderate to severe pulmonary hypertension [4]

Despite drug treatment it is impossible to restore lost lung function or stop disease progression; therefore, lung transplantation remains the only viable treatment for patients with end-stage COPD. The aim of the study was to determine whether patients with respiratory failure caused by COPD benefited from lung transplantation. The objective of the study was also to assess patients' pulmonary function after becoming lung recipients.

## MATERIALS AND METHODS

The retrospective study was carried out in the group of 69 patients (40 recipients, 11 patients still waiting on the list, and 18 patients who died while waiting on the lung graft). They were qualified to be treated by means of lung transplantation due to end-stage COPD in the Lung Transplant Program of Silesian Center for Heart Diseases between 2006 and 2018. The recipient group consisted of 13 women (32.5%) and 27 men (67.5%). Double lung transplantation (DLT) was performed in 23 patients (57.5%) and single lung transplantation (SLT) in 17 patients (42.5%). The qualification process of this facility required multiple assessments. During the qualification process, pulmonary function tests (PFTs) included spirometry (FEV1%) and forced vital capacity (FVC%) as well as arterial blood gases assessment. Measurements were taken during qualification and in the following months (1, 3, 6, 12,

18, and 24) after lung transplantation. Six-Minute Walk Test (6MWT) results (distance [m], Borg scale, and oxygen saturation (SpO<sub>2</sub> [%])) were checked during qualification. After the lung transplantation, survival was estimated with the Kaplan-Meier curve. The 2-year follow-up assessments were performed, including spirometry and 6MWT. The survival of patients who underwent transplantation was compared with patients who did not undergo lung transplantation. Follow-up also compared the results achieved by patients after SLT and DLT.

## Statistical Analysis

The Mann-Whitney *U* test,  $\chi^2$  test, and  $\chi^2$  test with Yates test were used, as appropriate. Kaplan-Meier curves were used for depiction of the survival time. Statistica 10.0 statistical software (StatSoft Inc, Tulsa, Okla, United States) was used for statistical analysis. All findings with *P* < .05 were considered statistically significant.

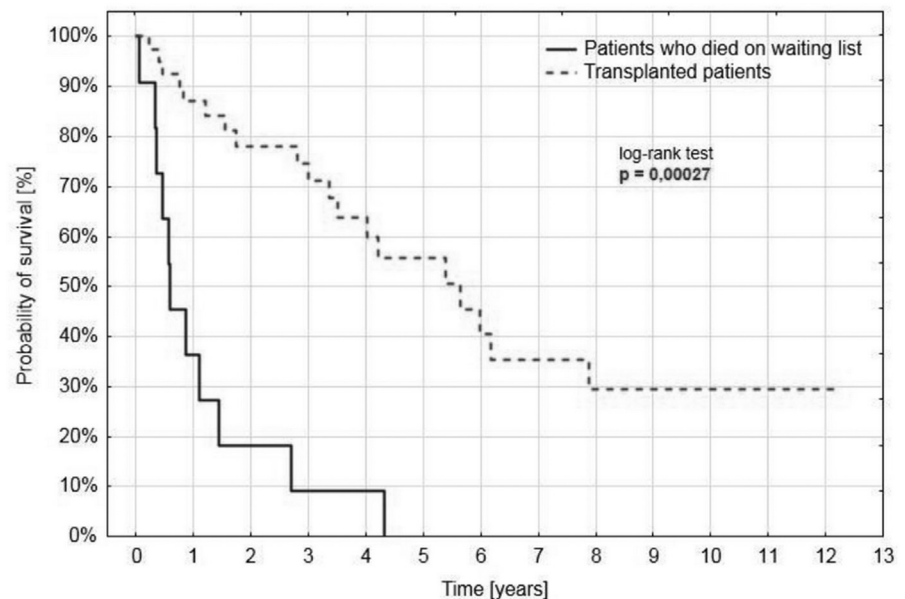
## RESULTS

Between 2006 and 2018, 69 patients with end-stage COPD were referred to the Silesian Center for Heart Diseases' Lung Transplant Ward and were finally qualified to be treated by means of lung transplantation. At qualification, patients obtained  $22.06 \pm 7.46\%$  of FEV1 predicted value. Percentage of predicted FVC reached higher values ( $47.80 \pm 17.79\%$ ). The 6MWT revealed that patients were able to walk  $158.08 \pm 66.52$  m on average. Effort performance was assessed as heavy ( $5.2 \pm 1.8$ ) on the 10-point Borg scale. However, mean oxygen saturation decrease was 8.92 percentage points with mean oxygen saturations before and after the test, respectively, of 97.92% and 79%. It is consistent with the fact that chronic lung diseases make patients more adaptable to insufficient oxygen supply.

There were 40 qualified patients who received lung transplantations. The remaining 11 patients died on the waiting list without the procedure. Statistical analysis showed no significant differences among those 2 groups at qualification.

Survival on the National Lung Transplantation Waiting List (NLTWL) was estimated with use of the Kaplan-Meier curve for all qualified patients. It shows that since official placement on NLTWL, 50% of graft recipients reached survival of 5.5 years. For comparison, our calculations show that qualified patients who did not undergo transplantation had 50% survival less than 1 year. Kaplan-Meier curve representing this part of the study was demonstrated in Fig 1.

Forty patients underwent lung transplantation as a treatment of end-stage COPD, among which 21 patients are alive. During the 12-year study period, 81.63% of qualified patients became transplant recipients. According to Pol-transplant statistics in Poland, the average waiting time for lung transplantation is 193 days [12]. The Kaplan-Meier survival curve of patients from the Lung Transplant Program of Silesian Center for Heart Diseases (total SLT and DLT) after lung transplantation is respectively estimated at 82% in 1 year, 61% in 3 years, and 51% in 5 years.



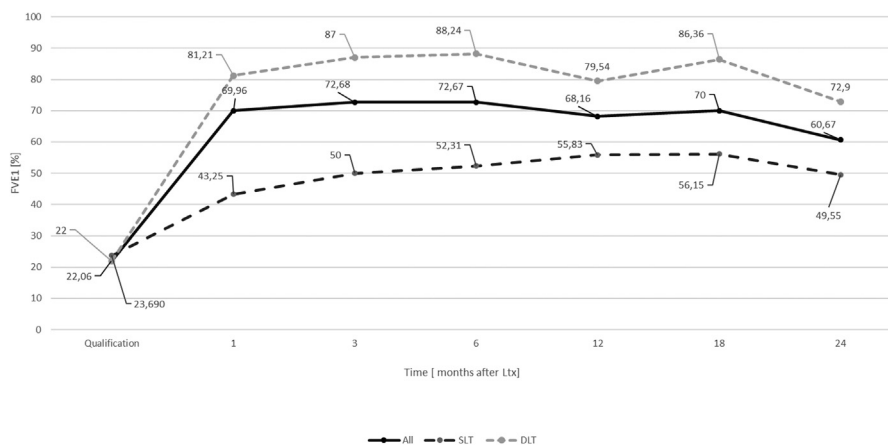
**Fig 1.** Survival on National Lung Transplantation Waitlist estimated by Kaplan-Meier curve. Survival curve of patients who did not undergo lung transplantation as well as lung transplant recipients.

During every check-up at the Silesian Center for Heart Diseases, patients have their graft function evaluated by spirometry and 6MWT. Improvement of their functional status is presented by means of FEV1% increase during 2 years of follow-up. Detailed depictions are shown in Fig 2. All graft recipients improved their FEV1 results; however, statistics show that patients after DLT, despite very similar results achieved during qualification, shortly after transplantation achieve much better results in spirometry than patients who had undergone SLT (81.21% in DLT patients vs 43.25% in SLT patients 1 month after procedure,  $P = .000073$ ). A similar relationship persists during follow-up (79.54% in DLT patients vs 55.83% in SLT patients 12 months after procedure,  $P = .037102$  and 72.9 in DLT patients vs 49.55% in SLT patients 24 months after transplantation,  $P = .006347$ ).

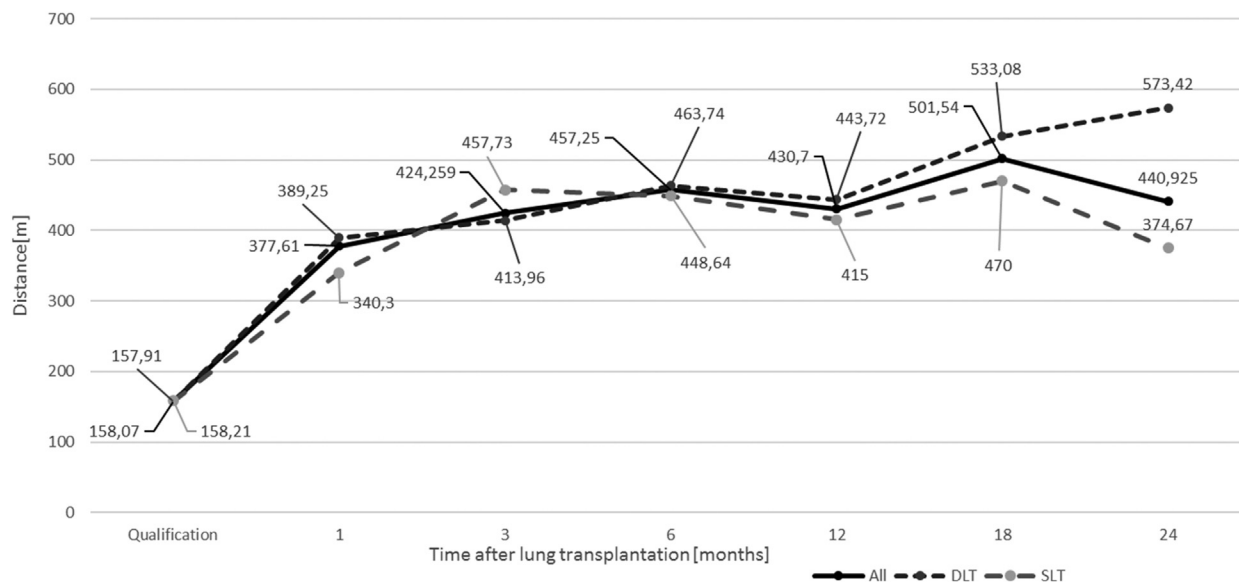
Statistics also show improved FVC results. During qualification the average FVC was 47.8 percentage points. One month after surgery, the values increased on average to 69.7%, 77.47% among DLT recipients and 51.25% among SLT recipients,  $P = .001264$ .

During 1 year of observation, results were increasing gradually in both groups: 66.42% in the SLT group vs 92.15% in DLT,  $P = .001069$ . After 2 years they reached values of 92% among DLT recipients and 59.72% in the SLT recipient group ( $P = .001264$ ).

Fig 3 shows that also in the 6MWT there was a change in results reached between qualification and after lung transplantation. For almost 18 months after procedure the results of patients with SLT and DLT were comparable, but 24 months after procedure we observed a major difference between SLT and DLT recipients. Patients after DLT



**Fig 2.** Results of Forced expiratory volume in 1 second achieved by patients during qualification and in the following months after lung transplantation. Division of patients depending on the type of SLT or DLT procedure. SLT- single lung transplantation DLT- double lung transplantation



**Fig 3.** Results of 6 Minute Walk Test achieved by patients during qualification and in the following months after lung transplantation.

obtained 573.42 m vs patients after SLT who obtained 374.67 m. This difference is statistically significant,  $P = .018540$ .

In addition to the distance on the 6MWT, we decided to check how the saturation changes before and after the test. At the qualification, the saturation decreased by almost 10%, and after transplantation the decrease in saturation was about 2% and remained at a similar level in the following months. Saturation changes in patients after SLT and DLT were similar. No statistically significant differences were observed.

## DISCUSSION

Lung transplantation remains the definitive treatment for end-stage lung failure, whereas COPD represents 1 of the leading indications for a transplantation [13]. According to the ISHLT registry from 2019, 50% survival after lung transplantation was estimated to be approximately 6 years. These results were even better after assessment of survival conditional to 3 months survival, as it reached 7 years. In terms of average survival among SLT and DLT recipients, the results are approximately 5.5 and 7 years, respectively [14].

Zerriouh et al analyzed the consecutive outcomes of 88 patients undergoing lung transplant for COPD, excluding patients with alpha-1 antitrypsin deficiency (A1ATD). They noted a 6-year survival of 57%, which is comparable to that described in the ISHLT registry [15]. Pochettino et al in their observations reported that average survival 5 years after transplantation was 61.9% for DLT and 57.4% for SLT [16]. Lahzami et al reviewed all consecutive subjects who underwent single or bilateral LTx (SLT and

DLT, respectively) for COPD at Lausanne and Geneva University Hospitals (subjects with COPD related to A1ATD were excluded from the study). The median post-transplant survival was 6.3 years [17]. Graft recipients with COPD from the Lung Transplant Program of Silesian Center for Heart Diseases (total SLT and DLT) achieved 50% survival in 5.5 years. The results obtained in our center do not differ from the global results described by ISHLT (50% survival in 6 years). One-year survival was achieved by more than 82% of patients after transplantation in our research; for comparison Pochettino et al [16] estimated 1-year survival at 82.6% for DLT and 72.2% for SLT recipients, whereas Lahzami et al [17] reported survivability at 77%.

In the 2-year survival period after transplantation, we recorded a decrease of almost 10% (survival is about 72%). The same results were found in a 2-year observation by Lahzami et al [17]. For comparison De Meester et al from the Netherlands [18] described 2-year survival among 56% of COPD patients (including COPD-related A1ATD). In our center double lung recipients at qualification were able to obtain 23.7% of their predicted FEV1; at 12 months after lung transplantation, such percentage was approximately 77.5%. Single lung recipients at qualification reached an average FEV1 of 22%; within 12 months after transplantation this value increased to 55.8%. Those results were similar to those reported by Pochettino et al [16], whose patients presented similar FEV1% at qualification and reached approximately 80% of predicted FEV1 among DLT, compared with 50% of predicted FEV1 following SLT at 12 months after lung transplantation. For FVC, recipients at qualification for SLT and DLT obtained 55.9% and 40.9%, respectively, predicted value. FVC results were 66.4% for



SLT and 92.1% for DLT recipients at 12 months after lung transplantation. Findings from Pochettino et al. [16] indicate the results obtained 1 year after surgery among their studied group were 90% predicted FVC value among DLT and 65% of the same parameter among SLT recipients.

The results presented indicate that throughout the entire post-transplant follow-up period, the FEV1 and FVC reached following DLT was significantly higher than that obtained following SLT. This is also confirmed by the results presented by Thabut et al from France [19], who reported that survival benefit was greater with DLT than with SLT in patients with respiratory failure determined by COPD (median survival time after bilateral lung transplantation was longer than that after SLT, 6.41 years vs 4.59 years, respectively). Lung transplantation not only improves spirometry, but it is primarily an improvement in their fitness, which is best demonstrated by comparing the distance achieved before and after lung transplantation in 6 MWT. As previously described, the average distance extension in 6MWT in our center was an average of 282.86 m after 2 years (this is a threefold increase compared to qualifications). Pochettino et al [16] showed that at all post-transplant time points, the mean 6 MWT distance covered was higher following DLT than for SLT, with the difference ranging from approximately 100 to 400 feet (30.48 m to 121.92 m) (1 foot is approximately 0.3048 m).

## CONCLUSIONS

Lung transplantation extends the life of a patient with end-stage COPD, even if life expectancy is shorter than statistics indicate. In addition to survival time, respiratory efficiency is also improved, as demonstrated by the results of functional tests. According to studies, DLT is more beneficial for patients with end-stage COPD than SLT.

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